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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/780,484	02/17/2004	David B. Rozema	25771 US1	2135
83890	7590	01/26/2010		
ROCHE MADISON INC. 465 Science Drive Suite C MADISON, WI 53711			EXAMINER EPPS-SMITH, JANET L.	
			ART UNIT 1633	PAPER NUMBER
			MAIL DATE 01/26/2010	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/780,484

Applicant(s)

ROZEMA ET AL.

Examiner

Janet L. Epps-Smith

Art Unit

1633

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 October 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 3, 4, 6, 7, 10-13 and 15-20 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 3, 4, 6, 7, 10-13 and 15-20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/808)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.
2. Claims 1, 3-4, 6-7, 10-13 and 15-20 are presently pending.

Response to Arguments

Claim Rejections - 35 USC § 103

3. Claims 1, 3-4, 6-7, 10-13 and 15-20 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff (WO200075164 A1), in view of Mathiowitz et al. (US 6248720) and Haines et al. (US6479464).
4. Applicant's arguments filed 10/14/2009 have been fully considered but they are not persuasive. Applicants traversed the instant rejection on the grounds that the Wolff et al. reference teaches away from covalent attachment of nucleic acid to a polyamine, and further that the Wolff et al. reference does not teach the reversible modification of the polyamine.

Contrary to Applicant's assertions, page 25-26 of Wolff et al. clearly specifies compounds of the formula A-B-C, wherein A is a biologically active compound, such as a nucleic acid, B is a labile linkage that contains a pH-labile bond, and C is a compound that modifies the activity, function, delivery, transport,.....and sub-cellular targeting of the biologically active compound. Moreover, page 36, lines 25-33, defines "a labile linkage as a chemical compound that contains a labile bond." Furthermore, the reference teaches that "[a] labile bond is a covalent bond that is capable of being selectively broken. That is, the labile bond may be broken in the presence of other

covalent bonds without the breakage of other covalent bonds.” Furthermore, page 32 of this reference describes transfection reagents that mediate entry of oligonucleotides/polynucleotides into cells, this reference includes polyamines, and peptides such as membrane active compounds such as mellitin described on page 38. Additionally, page 59, lines 10-14, teach the following examples of membrane active peptides modified via labile linkage with a compound that inhibits the membrane activity of the peptide:

- 10 Preferred embodiments include 2,3-dimethylmaleamic-mellitin, 2-propionic-3-methylmaleamic mellitin, 2-propionic-3-methylmaleamic KL3, and 2,3-dimethylmaleamic-mellitin, which are membrane inactive compounds that become membrane active under acidic conditions.

5. Applicant's did not address the combined teachings of the cited references, and has only addressed the teachings of the Wolff et al. reference. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

6. Applicants have not provided sufficient evidence to support their assertions that the combined teachings of the cited reference would not have rendered the claimed invention obvious. As stated above, page 25 clearly disclosed the covalent attachment of a biologically active compound to a compound that modifies delivery, function, and transport of the biologically active compound. The reference further teaches that among those compounds that are use for modifying the delivery, function, and transport

of the biologically active compound, includes (*inter alia*) membrane activity peptides, wherein said peptides have been modified such that the membrane active peptides become active under acidic conditions (See page 59, lines 10-14).

7. Contrary to Applicant's assertions, it would have been obvious to the ordinary skilled artisan to modify the "C" portion of the A-B-C compounds of Wolff et al. as set forth on pages 25 of this reference, with the membrane active compounds of Mathiowitz et al. and Haines et al. since these references teach the usefulness of polymers such as polyvinylether (Mathiowitz et al.) and paradaxin (Haines et al.) in the transfection of nucleic acids into cells. Therefore, it would have been obvious to substitute art recognized nucleic acid transfection polymers for the polymers described in Wolff since the prior art polymers are disclosed as functionally equivalent to those polymers described in Wolff. See MPEP § 2144.06 [R-6].II., which describes the obviousness of substituting equivalents known for the same purpose.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1, 3-4, and 6-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the following:

1. (currently amended) A composition for delivering a polynucleotide to a mammalian cell comprising a membrane active polyamine-polynucleotide conjugate wherein:
 - a) the polyamine has molecular weight greater than 10,000 daltons;
 - b) the polyamine is linked to the polynucleotide via a labile covalent bond; and,
 - c) ~~one or more~~ a plurality of amines on the polyamine are reversibly modified by attachment of functional carboxyl groups via pH labile covalent bonds to form a negatively charged polymer wherein breakage of the pH labile covalent bonds in response to a decrease in pH results in cleavage of the functional carboxyl groups from the polyamine and restoration of the amines on the polyamine.

10. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 1 recites the broad recitation a labile covalent bond, and the claim also recites pH labile covalent bonds which is the narrower statement of the range/limitation.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Smith whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Weitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Smith/
Primary Examiner, Art Unit 1633